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A first approach to a neuropsychological screening tool using eye-tracking for
bedside cognitive testing based on the Edinburgh Cognitive and Behavioural ALS
Screen

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Abstract

Objective: Reliable assessment of cognitive functions is a challenging task in amyotrophic lateral sclerosis (ALS) patients unable to speak and write. We therefore present an eye-tracking based neuropsychological screening tool based on the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), a standard screening tool for cognitive deficits in ALS.

Methods: In total, 46 ALS patients and 50 healthy controls matched for age, gender and education were tested with an oculomotor based and a standard paper-and-pencil version of the ECAS.

Results: Significant correlation between both versions was observed for ALS patients and healthy controls in the ECAS total score and in all of its ALS-specific domains (all $r > 0.3$; all $p < 0.05$). The eye-tracking version of the ECAS reliably distinguished between ALS patients and healthy controls in the ECAS total score ($p < 0.05$). Also, cognitively impaired and non-impaired patients could be reliably distinguished with a specificity of 95%.

Conclusion: This study provides first evidence that the eye-tracking based ECAS version is a promising approach for assessing cognitive deficits in ALS patients who are unable to speak or write.

Keywords: Eye-tracking; Cognition; Edinburgh Cognitive and Behavioural ALS Screen; Amyotrophic Lateral Sclerosis; Motor Neuron Disease

Introduction

It is well recognized that cognitive deficits play a prominent role in amyotrophic lateral sclerosis (ALS) with about 30% of patients exhibiting impairment, mostly in the domains of language, verbal fluency and executive function (1-3). These deficits in addition to changes in behavior like disinhibition or apathy which also occur in a small subset of ALS patients (2) are associated with carer burden (4), survival (5) and decision making regarding life-shortening and prolonging measures (6-8). Therefore, a regular valid assessment of cognitive functioning, especially in the context of clinical scenarios in which decisional capacity is of utmost importance, is essential in the course of the disease (9).

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) is a widely used and well validated tool to screen for potential cognitive deficits among ALS patients in the domains of memory, visuospatial perception, language, verbal fluency and executive function as well as for behavioral changes (10,11). It is adapted to motor impairment, as it can be performed in a written or oral manner. However, in more advanced stages when patients lose the ability to speak or write, other techniques are needed. One promising approach is based on eye movements. Even though oculomotor impairments may occur in some patients in the course of ALS (12-14), for many patients it still has the potential to be a valuable tool in the detection of cognitive deficits. Previous studies have already proven the applicability of this approach for ALS patients (15-18), using different tasks of executive functioning and devices which require a stationary testing environment. Yet, a mobile version of a cognitive screening tool specifically designed for bedside use in ALS patients is still lacking.

Therefore, the goal of this study was to provide a proof of concept for a mobile eye-tracking screening tool based on the ECAS and to demonstrate its usefulness and

applicability in a sample of ALS patients. We hypothesized that the eye-tracking version is suitable to assess ALS patients' cognitive performance and to robustly identify those with relevant impairment.

Materials and Methods

Participants

The study was approved by the Ethics Committee of the University of Ulm (Reference No. 19/12) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave written informed consent to the study. Initially, 50 patients diagnosed with ALS according to the revised El-Escorial criteria (19) were recruited from the in- and outpatient clinic of the Department of Neurology, University of Ulm, Germany. An additional group of 50 healthy controls (HC) matched for age, gender and education was used for comparison. None of the participants had a history of any major psychiatric or neurological condition (other than ALS) and all subjects had normal or corrected to normal vision.

All patients were able to complete the paper-and-pencil ECAS version. However, due to insufficient control over the eye-tracking device, which was not due to ALS-dependent oculomotor impairments but rather discomfort with the unfamiliar technique, oculomotor recording was not possible in two patients. Additionally, one patient was not able to complete the eye-tracking based ECAS due to difficulties in task comprehension, whereas another wished to abort the experiment because of fatigue. Therefore, data of $n = 46$ patients were included in the final analyses. Patients' physical impairment was assessed using the ALS functional rating scale

revised version (ALS-FRS) (20), affective state was measured with the ALS Depression Inventory 12 (ADI-12) (21) and the proposed clinical ALS disease staging system from Roche et al. (22) was used for further patient characterization. For detailed sample characteristics see Table 1.

Design

A pseudo-randomized study design similar to the one previously reported by Keller et al. 2015 (16) was used: To avoid sequence effects, patients and HC were each subdivided into two age- gender- and education-matched groups. One group completed the German paper-and-pencil ECAS version (23) according to standard procedures first, followed by the eye-tracking based version, whereas the other group did vice versa. Testing was scheduled to take place on the same day.

Eye-tracking based ECAS

To reduce fatiguing testing time and to make the eye-tracking based version suitable for oculomotor control, the German ECAS version from Lulé et al., 2015 (23) was modified, incorporating all five original domains (ALS-non-specific: memory, visuospatial perception; ALS-specific: language, verbal fluency and executive function). Detailed information about this version can be found in Table 2.

Tasks were displayed on a PC presentation screen, whereas the participants gave their answers by directing their gaze on a separate notebook screen displaying a matrix composed of numbers 0 to 9 and all letters of the German alphabet. Fixation of gaze for 1000 ms on a number or letter initialized selection of this item. Participants' eye movements were registered using the commercially available EyeTribe® system (The Eye Tribe Aps, Copenhagen, Denmark) connected to the notebook on which the matrix was displayed. Their choice was subsequently

recorded by in-house written software and displayed above the matrix (Figure 1). Following each selection, subjects had the possibility to correct their choice or were asked to confirm their answers for every question of the eye-tracking based ECAS. All answers were recorded on a separate sheet of paper by the experimenter and later used for calculating each subject's domain-specific and total eye-tracking based ECAS score (Table 2).

Statistical analysis

Data were a priori analyzed for normal distribution using the Kolmogorov-Smirnov test. In order to detect group differences between ALS patients and HC, Mann-Whitney U tests and, where appropriate, Pearson's chi-squared tests were used. Spearman-Rho correlation analyses were used to determine correlation coefficients between the two versions. A median split on patients' overall ECAS score in the standard version was performed to compare cognitively more and less impaired patients in the eye-tracking version. Also, performance accuracy of ALS patients and HC was calculated for both versions. All analyses were performed using IBM® SPSS Version 21.0, two-sided and the significance level was set at $p < 0.050$.

Results

Group comparisons

In the standard version of the ECAS, ALS patients performed significantly worse than HC in the ALS-specific domains of verbal fluency ($p = 0.002$), executive function ($p = 0.014$) and in the overall score ($p = 0.001$). In the eye-tracking version of the ECAS

they performed significantly worse in the executive function domain ($p = 0.007$) and in the overall score ($p = 0.030$) (Table 1).

The median of patients' overall performance accuracy was 82% in the standard version of the ECAS and 83% in the eye-tracking version. For HC it was 89% in the standard version and 87% in the eye-tracking version, respectively. ALS patients' scores did not significantly differ between testing modalities in the ECAS overall score and any of its domains except verbal fluency ($p = 0.001$). For HC there was no difference in scores of any ECAS domain or the total score between testing modalities.

The comparison between high and low performing patients as determined by the median split based on patients' overall ECAS score in the standard version revealed a significant group difference in the executive function domain ($p = 0.007$) but no significant difference in the ECAS overall score ($p = 0.090$) of the eye-tracking version.

Correlation analyses

In the patient sample, Spearman-Rho correlation analyses revealed a statistically significant congruence between results in the standard and eye-tracking version of the ECAS in the domains of visuospatial perception ($r = 0.379$; $p = 0.009$), language ($r = 0.728$; $p < 0.001$), verbal fluency ($r = 0.313$; $p = 0.034$), executive function ($r = 0.520$; $p < 0.001$) and in the total score ($r = 0.393$; $p = 0.007$) (Figure 2A & 2C). In the memory domain however, this correlation was still acceptable but did not reach the threshold for statistical significance ($r = 0.288$; $p = 0.052$). Similar correlations between the standard and eye-tracking version of the ECAS were also found in the HC sample in all domains (memory ($r = 0.322$; $p = 0.023$), visuospatial perception ($r = 0.374$; $p = 0.007$), language ($r = 0.543$; $p < 0.001$), verbal fluency ($r = 0.473$; $p =$

0.001), executive function ($r = 0.645$; $p < 0.001$) and in the total score ($r = 0.602$; $p < 0.001$) (Figure 2B & 2D). There was no statistically significant association between physical impairment as measured by the ALS-FRS and patients' cognitive performance in both ECAS versions as well as between their depressiveness as assessed by the ADI-12 and their performance in any domain of the two versions.

Specificity and sensitivity

Using a cut-off score for cognitive impairment in ALS patients, determined according to the ECAS guidelines by Abrahams et al. 2014 (10), a specificity of 95% and a sensitivity of 50% were found for the total score of the eye-tracking version of the ECAS. For the language domain of this version, specificity was 100% and sensitivity 80%. In the verbal fluency domain, specificity was 100% and sensitivity 50%, and in the executive function domain, specificity and sensitivity were 98% and 33%, respectively.

Discussion

This study shows the feasibility and reliability of a mobile eye-tracking screening tool based on the ECAS which can be easily administered even at the patient's bedside in a time frame of usually less than one hour. As in previous studies with healthy subjects (15,24,25) and ALS patients (16), there was a strong association between performance in both modalities of cognitive testing (oculomotor and paper-and-pencil) with satisfying correlations between scores in all relevant domains of both versions of the ECAS in the healthy control and in the patient sample.

Results obtained with the eye-tracking based ECAS version also allowed to distinguish between patients and healthy controls in the domain of executive function and in the ECAS total score as well as between more and less cognitively impaired patients in the executive function domain. However, there was no significant difference between ALS patients and healthy controls in the other ALS-specific domains (language and verbal fluency). For the language domain this is not surprising, as in this sample there was no group difference in the standard version of the ECAS either. For the verbal fluency task however, in which patients performed significantly worse than healthy controls in the standard ECAS, this might be due to the testing modality: During spelling of one word with the eyes, subjects might additionally find time to imagine the next word already; but it could also be explained by the applied changes compared to the original ECAS, i.e. using only the restricted word generating task with subsequent weighting to reduce fatiguing testing time.

This, of course, can be generalized to all domains that required amendments for oculomotor based testing. Specifically, the reduction of items in the language and verbal fluency domain might hamper comparability between both modalities. Yet, using all items of the standard ECAS would have resulted in a too time consuming and tedious oculomotor testing, which made this tradeoff between elaborateness and usability necessary. To increase the reliability of the eye-tracking paradigm we introduced weighting factors which ensure a score distribution equal to that of the standard ECAS. Given these issues, alternative approaches to assess potential deficits in these patients could use more simplistic, domain-specific tasks (18). However, our goal was to implement an oculomotor based screening tool encompassing a broad range of potential cognitive deficits associated with ALS and not a diagnostic instrument for one specific cognitive task only.

The very high specificity observed in the most relevant cognitive domains and in the ECAS total score provides evidence that the eye-tracking based ECAS version is well suited to identify those ALS patients with substantial cognitive impairment. Yet, the price for this high specificity is a rather low sensitivity and the accompanying higher risk for potential type II errors in some domains of this version. Whereas this screening instrument therefore seems to have a very low rate of false positive results, caution should be applied with regard to potential false negative results. Again, this can be tolerated as the main focus of this eye-tracking based screening tool is to identify those ALS patients with severe cognitive impairment.

Due to the nature of this proof-of-principle study, no far advanced ALS patients were included. Even though cognitive impairment seems to be stable during the course of the disease (26,27) and even may precede motor symptoms (28), further studies are needed to investigate the cognitive status of ALS patients in advanced stages of the disease. Despite using a balanced pseudo-randomized order in our study design, there might also have been some learning effects, potentially distorting the results of both versions in the memory and verbal fluency domain. However, for our purposes this could not have been avoided. Another limitation of this approach certainly is that patients are required to still have sufficient eye movement control. Yet, studies have reported abnormalities in oculomotor control in the course of ALS (12,14,29) which may, especially in far advanced patients due to extended alterations in neural networks (30), lead to a complete loss of voluntary eye movements in the final stages of ALS. Future work in this field could therefore focus on developing tools based on brain-computer-interface control, a promising technique whose usability for these ALS patients has already been demonstrated in previous studies (31,32), to reliably assess cognitive functioning in far advanced patients (33). However, above mentioned considerations regarding the translation of standard neuropsychological

screening instruments into an eye-tracking format also apply when this modality of testing will be used. Furthermore, a more thorough psychometric validation of a specific eye-tracking version of the ECAS in a sample of healthy participants is needed to establish this tool for use outside research paradigms.

In conclusion, this approach provides support that eye-tracking based techniques can be used as a fast and reliable method for cognitive assessment of patients unable to speak and write based on the ECAS, an established neuropsychological screening tool specifically designed for ALS, which in its standard form has already been well validated and widely used in different cultures and languages (10,19,34,35). Considering the fact that information about the cognitive status of ALS patients plays a crucial role in the context of therapeutic interventions and end-of-life decision making (6,7,9), the importance of ALS-specific hand- and speech-motor-free cognitive testing becomes even more apparent.

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Declaration of interest

The authors declare no competing interests.

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Figure 1: Illustration of the eye-tracking version of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

Setup of the eye-tracking version of the ECAS including the presentation screen, on which the current task is displayed, and the main screen, on which the matrix to write the answer, composed of numbers 0 to 9 and all letters of the German alphabet, is presented. Participants' eye movements are registered by the EyeTribe® device. A letter or number on the matrix is selected by fixating the target for 1000 ms.

Figure 2: Correlations between performance scores of the standard and the eye-tracking based version of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

Shown are the total scores of the eye-tracking (ECAS ET) and the standard (ECAS STD) version of the ECAS (top row) for ALS patients (A; green) and healthy controls (B; blue) as well as the executive function scores of both versions (bottom row) for patients (C; green) and healthy controls (D; blue). Additionally, the correlation coefficient r , as determined by Spearman-Rho correlation analyses, is given.